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Signs of Activity and Progression in Chronic Glaucoma

by

Catharina Holmin



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Catharina Holmin

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The present thesis is based on the following publications:

- I Characteristics of manifest glaucoma in the early stages (in collaboration with B Bengtsson and C E T Krakau).
Glaucoma 2, 351-358, 1980.
- II Disc haemorrhage and glaucoma (in collaboration with B Bengtsson and C E T Krakau).
Acta Ophthalmol 59, 1-14, 1981.
- III Optic disc evaluation versus the visual field in chronic glaucoma.
Acta Ophthalmol 60, 275-283, 1982.
- IV Automatic perimetry in the control of glaucoma (in collaboration with C E T Krakau).
Glaucoma 3, 154-159, 1981.
- V Visual field decay in normal subjects and in cases of chronic glaucoma (in collaboration with C E T Krakau).
Albrecht v. Graefes Arch. Klin. Ophthalmol. 213, 291-298, 1980.
- VI Regression analysis of the central visual field in chronic glaucoma cases (in collaboration with C E T Krakau).
Acta Ophthalmol 60, 267-274, 1982.
- VII Short term effects of timolol in chronic glaucoma. A double blind study using computerized perimetry (in collaboration with C E T Krakau).
Acta Ophthalmol 1982. In press.

In the thesis, these papers are referred to
by their Roman numerals.

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INTRODUCTION

CHRONIC GLAUCOMA is a slowly progressive disease characterized by a gradual decrease of tissue in the optic nerve head with a corresponding functional loss recognized as areas of depressed sensitivity (defects) in the visual field. According to the generally accepted hypothesis this process is caused by some obstruction of the aqueous outflow. The intraocular pressure (IOP) consequently rises, causing disturbances of the circulation in the optic disc.

It follows from this hypothesis that the fundamental parameter in the detection and the follow up of glaucoma cases should be the IOP. The therapy is consequently obvious: the pressure has to be lowered in order to protect the optic disc from further damage.

This is an attractive and simple hypothesis which might have been acceptable, had not reality been a bit less stream-lined.

It appears from the results of large-scale population studies (Hollows & Graham 1966; Linnér & Strömberg 1967; Nørskov 1970; Perkins 1975; Nelleman-Sørensen et al 1978) that it is impossible to claim a fixed level as the dividing line between normal and pathological pressure. Furthermore, it is well known that the glaucomatous process may develop in spite of apparently well regulated pressure. According to a widespread opinion some optic discs, due to vascular changes, are abnormally vulnerable and consequently unfavourably affected even by statistically normal or even low pressures. Thus the critical or "normative" pressure for the individual eye may fall within or even below the normal range. A further explanation of the progression of damage in spite of well controlled pressure is that a "point of no return" in the glaucomatous process has been reached.

Even if such ad hoc hypotheses may save the pressure theory, the IOP is unsatisfactory as a decisive criterion in the treatment of glaucoma. Obviously we have to rely on other signs in the detection and control of glaucoma. However, whereas it has been

possible to measure the IOP in a fairly simple and accurate way, the evaluation of the optic disc is to a large extent a subjective matter (Lichter 1976) and techniques for a sufficiently objective recording of the functional damage in the slowly progressive process have not been available.

The recording of visual fields (perimetry) has traditionally been obtained by manual methods involving a great deal of subjectivity on the part of the perimetrist. The introduction of computerized perimetry, however, implies that the condition of the visual field is measured in a more objective and standardized manner. A further advantage is that the results are obtained as numerical values, thus admitting of statistical calculations on series of visual fields. Hence the comparison of functional and morphological changes can be made more accurately and the progression of the visual field defects can be defined with more precision. These factors facilitate a discussion of the pressure hypothesis.

The present studies profit from these methodological advantages and are mainly based on an extensive use of computerized perimetry. The perimeter used is the Competer, which has proved to be sensitive in the detection of glaucomatous field defects (Heijl 1976). This method has also been shown to surpass manual perimetry in reproducing defects (Gramer et al 1979).

The first three papers to be summarized mainly concern the morphological signs of the optic disc and the corresponding changes in the visual fields, which make it possible to recognize with some certainty cases of chronic glaucoma. The following four papers principally concern the development of the functional changes. Although the testability of the pressure hypothesis is restricted for ethical reasons, the aim has been to elucidate to some extent the relation between the IOP and signs of activity in the glaucomatous process as reflected by disc haemorrhages and by decay of the visual field.

MATERIALS AND METHODS

Computerized perimetry as applied here has been extensively described elsewhere (Heijl & Krakau 1975; Krakau 1978). The testing is performed at 64 test points in a circular pattern covering the central visual field.

Each test light - a light emitting diode - can be lit at 16 levels of intensity. The intensity ratio between two adjacent levels is 1:2, with the highest intensity at the zero level.

The exposure time was 0.5 s and the max. reaction time 2.0 s. The background illumination was either 0.1 or 1.0 cd/m^2 in the earlier studies (I,IV,V), but when more powerful test lights had become available 1.0 cd/m^2 was used exclusively.

The fixation is checked by projecting a test light at random instants on to the blind spot area. If the patient keeps his fixation this light cannot be seen.

The results are printed out in numerical values in a diagram. To make scotomatous areas stand out clearly, the modal value of the threshold is put at 0, and the negative deviations from the modal value which signify defects are stressed by the addition of a number of zeroes.

Two test programs were used. According to the threshold program, the threshold values in all 64 test points are estimated. They are tested according to a staircase technique, i.e. when a light is seen, it will next time be shown at a level one step lower in intensity, and vice versa. The testing starts at 4 test points on the 10^0 circle and their threshold values are taken as the starting level for neighbour points.

According to the screening, just as in the threshold program, the thresholds at the 4 test points in the 10^0 circle are determined initially, the rest of the test points then being tested on a supraliminal level.

The test session for each eye lasts about 10 min. with the threshold and about 3 min. with the screening program.

With the screening program a defect was defined as $\geq$ one test-point $>$ one step lower than the supraliminal starting level. With the threshold program the minimal requirement of a defect was an area with > 2 points > 2 steps below the modal value.

The material in these studies is mainly derived from the glaucoma care unit in Lund. Some of these patients - in publication I the whole material - were among those discovered in the course of a population survey carried out with computerized perimetry at Dalby, Sweden, by Dr B. Bengtsson.

The Dalby survey was also used for the estimation of the normal visual field decay in publication V as well as for certain estimations in publication II.

In publication III the material was taken from a multicenter glaucoma study.

The materials are further specified in the presentations of the various studies.

CHARACTERISTICS OF MANIFEST GLAUCOMA IN THE EARLY STAGES (I)

In a population survey comprising 1511 individuals in the ages between 55 and 70, 15 cases (18 eyes) were considered chronic glaucoma (Bengtsson 1981). The diagnosis "manifest glaucoma" was based on the presence of visual field defects spotted by computerized perimetry (screening) and not otherwise explained. These cases were previously unknown and there were reasons to consider them as largely representing early stages: subjective symptoms were lacking, the IOP was in half of them below 20.5 mmHg and the defects were often so small that they might have been missed at routine manual perimetry. These cases were found to deserve close study which might answer two questions: was the diagnosis well founded; and what is the probable course of the further development?

Methods

Computerized perimetry, ophthalmoscopy, fundus photography and applanation tonometry were performed at intervals of usually about 3-4 months. Stereoscopic funduscopy was used in every case but not at every visit. Impairment of the visual field was assumed when new defect points appeared at renewed screening sessions.

Results

Out of the original visual field defects, 13 consisted of circumscribed scotomata or small arcuate defects not connected with the blind spot, and 5 consisted of arcuate defects connected with the blind spot. A connection with the blind spot was later established in 3 additional cases and in one case a small defect appeared in the second eye. In all, progression of visual field defects was documented in 5 out of 10 patients observed more than one year.

A loss of tissue in the optic disc corresponding to the visual field defect was always found, in general as a polar notch. In two cases, incomplete notches (notches not reaching the disc

margin) developed into complete ones during a follow-up of 2 years. This development was accompanied by progression of the field defects. The patient, whose defect appeared in the second eye during the observation, had marked saucerization of both discs at detection.

Disc haemorrhages were frequent findings. Altogether, 24 separate disc haemorrhages were observed. In 10 patients at least one haemorrhage was ascertained, repeated haemorrhages were found in 5 eyes. The haemorrhages were often located just temporally to polar notches though 5 haemorrhages (in 5 eyes) were situated far from any marked loss of neural tissue.

In general the IOP was low at detection, but all eyes with field defects, followed for more than one year, had at least one pressure reading above 20.5 mmHg. Except for 2 cases (one with pseudoexfoliations and another with a glaucoma secondary to chronic uveitis) with pressures exceeding 40 mmHg at the detection, no single pressure reading exceeded 30 mmHg.

Discussion

In all eyes with field defects a corresponding loss of tissue in the optic disc was found. Two of the three major criteria in the diagnosis of glaucoma were thus fulfilled.

The third major criterion - a high IOP - has become predominant in the concept of glaucoma. Consequently there is a tendency to consider cases with a certain pressure, say below 21, as a separate group, etiologically different from those with higher pressures. In half of the present material the IOP was below 20.5 mmHg at detection and the diagnosis "low tension glaucoma" would have been a natural choice. The further development, however, demonstrated that such a distinction would have been unwarranted.

Disc haemorrhages - indicating an active process - were surprisingly frequent findings among these cases. Occasionally, the haemorrhages occurred in apparently normal areas and without corresponding field defects. This may, of course, be due to inability to detect very small defects and minor losses of tissue in the optic nerve head. On the other hand, a haemorrhage might

be the very first sign of the glaucomatous process and actually precede other signs of damage.

Chronic glaucoma is a slowly progressive disease. In these cases signs of activity in the shape of disc haemorrhages and/or progression of field defects were found in 9 of 10 cases observed for more than one year. Objections might be raised to the somewhat crude way of evaluating the development of the visual field defects. Nevertheless, this evaluation was not contradicted by the further development (outside this study) based on a more strictly quantitative trend analysis.

Conclusions

No obvious objections to the diagnosis "chronic glaucoma" in the cases spotted by computerized perimetry could be raised.

A separation into subgroups would have been unwarranted, since on the contrary the uniformity of our findings was impressive. The intraocular pressures were persistently concentrated around the conventional dividing-line between normal and pathological pressures, and there was a striking coincidence of field defects, haemorrhages and substance defects in the optic disc.

The great number of disc haemorrhages was a surprising finding which invited further study. In the following paper (II) devoted to disc haemorrhages the implications of this finding will be discussed on the basis of these and other cases.

*

DISC HAEMORRHAGE AND GLAUCOMA (II)

The present study of the natural history of disc haemorrhages is based on a) the glaucoma group presented in publication I; b) cases - not necessarily diagnosed as glaucoma - with disc haemorrhages.

The material comprised all cases with at least one disc haemorrhage detected in 1) Dalby, at the survey and in the follow-up of the glaucoma cases; 2) the glaucoma care unit in Lund during

about the last 2 years. A total of 127 disc haemorrhages in 51 patients (66 eyes) was observed.

Results and discussion

An analysis of the Dalby population made it possible to clarify two important aspects: the frequency of haemorrhages in a sample of chronic glaucoma cases and the frequency of glaucoma in a sample of cases with disc haemorrhages.

Frequency of glaucoma in "bleeders"

In the Dalby survey including 1511 persons (age 55-70) all discs were examined in two independent ways: by ophthalmoscopy and by fundus photography. Thus it seemed reasonable to assume that we recognized a majority of all disc haemorrhages beyond a certain size and thus detectable at this occasion.

In 12 cases a disc haemorrhage was observed at the initial examination. Six of these had a field defect in the same eye. One case with a field defect in one eye and a disc haemorrhage in the other later developed a defect in the other eye as well. In the remaining 5 cases the initial visual field screening was negative and only one had an IOP > 20.5 mmHg. One of these died a few months after the survey, 3 later developed definite visual field defects.

Frequency of "bleeders" among glaucoma patients.

The disc haemorrhages were symptomless and transitory and were generally resorbed without leaving any detectable traces. More often than not, most "bleeders" were free of haemorrhages. The proportion of "bleeders" in a population has therefore to be assessed on the basis of a large number of adequately spaced observations of all members that have not already had at least one disc haemorrhage.

Fifteen cases with glaucomatous visual field defects were detected in the survey. They are presented in publication I in which haemorrhages were ascertained in 10 cases. In 11 of the 15 cases at least one disc haemorrhage was detected within the course of 10 visits. In one additional case a disc haemorrhage was observed at the twelfth visit. The remaining 3 cases without haemorrhages were all observed at least 10 times.

FIELD
DEFECTS

DISC
HAEMORRHAGES

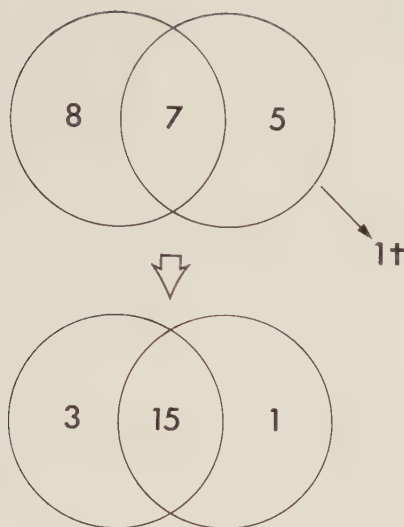


Fig. 1.

20 cases in the Dalby population had field defects and/or haemorrhages at the survey (top). The findings during the subsequent course demonstrates a growing coincidence between these two symptoms (below).

The relationship between field defects and disc haemorrhages detected in the Dalby population is summarized in fig. 1.

*

The following results are based on the whole material.

Anterior segment and IOP in "bleeders"

Disc haemorrhages were found in eyes with pressure reducing therapy as well as in those without. Further, a well regulated IOP did not seem to provide protection against disc haemorrhages (Fig. 2). Neither were disc haemorrhages restricted to a special low-tension glaucoma group since in 55 of the 66 eyes at least one pressure reading ≥ 21 mmHg had been recorded.

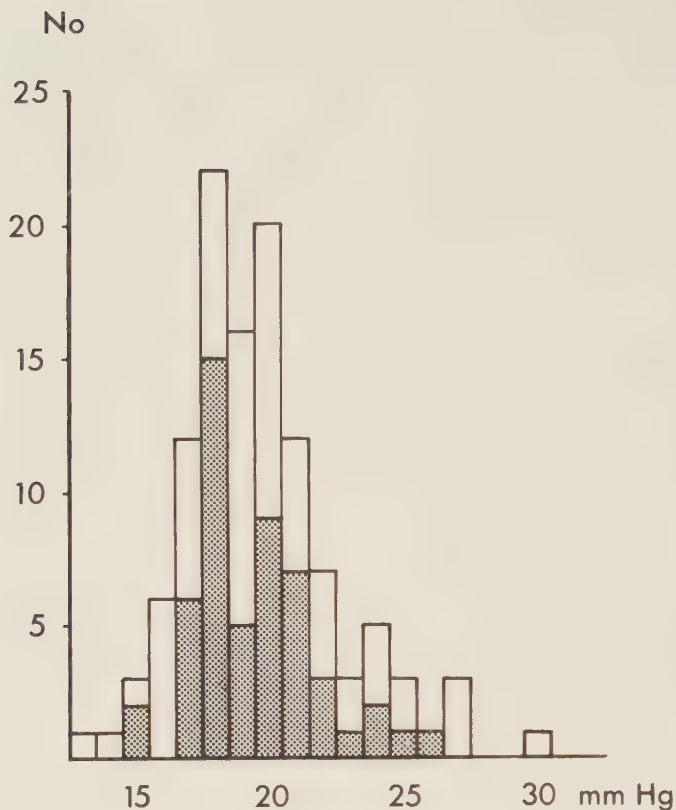


Fig. 2.

Frequency histogram of IOP at the detection of a haemorrhage. Empty bars: 64 pressures during non-treatment (42 eyes); dotted bars: 52 pressures during treatment (28 eyes). (In 4 eyes haemorrhages were detected both during treatment and non-treatment).

Few pathological changes were present in the anterior segment. However, cases with exfoliations (8), narrow angles (2) and post-uveitic gonio synechiae (1) were represented.

Appearance and localization of haemorrhages

The shape and the size of the haemorrhage varied considerably. Small haemorrhages, only detectable by close examination, as well as large flame-shaped ones were seen. Some large disc haemorrhages bore so close a resemblance to those seen in cases of retinal vein occlusion that a kinship between these two conditions seemed likely. Further support for this idea was

furnished by the occurrence of a retinal vein occlusion in 4 cases.

The haemorrhages were distributed over the whole disc circumference, though with a preponderance in the polar regions. In an analysis of the relation between the location (clockwise) of the haemorrhage and the state of the corresponding half of the visual field, indications of a connection between polar haemorrhage and very small or no defects were found, whereas haemorrhages corresponding to larger defects tended to be located more temporally. This is in accordance with the observation that haemorrhages appear where papillary substance is available; the substance defects generally start as notches in the polar region and, consequently, the haemorrhages tend to avoid this region in the more advanced cases.

Age and sex distribution

Above the median age (67 years) men were as common as women. However, a significant but unexplained overrepresentation of women was found in the group below the median age (22 women, 3 men).

Conclusions

Disc haemorrhages are common signs in chronic glaucoma. Among 15 glaucoma cases 12 showed haemorrhages and among 17 cases with haemorrhages, 15 cases had, or developed later, field defects. Thus it seemed likely not only that most cases of chronic glaucoma have disc haemorrhages at one time or another, but also that most "bleeders" have active glaucoma.

Disc haemorrhages seemed to be connected with progression of defects in the optic disc and the visual field though their effects are not immediately recognized.

No support for the idea that a well controlled pressure provides protection against haemorrhages was found.

*

In the description of the optic discs in the glaucoma group from the Dalby survey a simple classification was found convenient. This classification was largely based on signs described by Read & Spaeth (1974). The basis of the present evaluation was a thorough clinical examination including i.a. stereoscopic funduscopy. Bias due to other clinical data, e.g. the visual fields, cannot be precluded. The aim of the study presented in publication IV was to estimate the agreement between the condition of the optic disc and the visual field obtained by computerized perimetry. Further, the consistency was tested between different observers in using the classification referred to.

OPTIC DISC EVALUATION VERSUS THE VISUAL FIELD IN CHRONIC GLAUCOMA (III)

Material and methods

In order to allow an unbiased evaluation carried out by several observers, disc photographs of cases with which the observers were unaquainted were used. Thirty-two single colour photographs, routinely obtained, of eyes with glaucomatous field defects were mixed with 8 photographs of fellow eyes. Three independent observers examined the photographs and due to the asymmetry within the glaucomatous visual field the upper and lower half of the disc was evaluated separately. The following classification was used: normal rim (0), saucerization (1), narrow rim (2), incomplete notch (3), complete notch (4), and a more extensive loss of tissue reaching the disc margin (5) (Fig. 3). Further, the occurrence and localization of disc haemorrhages were denoted.

In the examination of the visual fields, defects were found in 41 of the 80 field halves. By a simple quantification of the defects with respect to the number of test points included, a separation in small ($n = 22$) and large ($n = 19$) defects was made. The small defects were mainly shallow scotomata, whereas most of the large defects were more or less dense arcuate defects.

Results and discussion

A correspondence between the disc and the visual field (defined as number of true negatives + true positives/total number) was

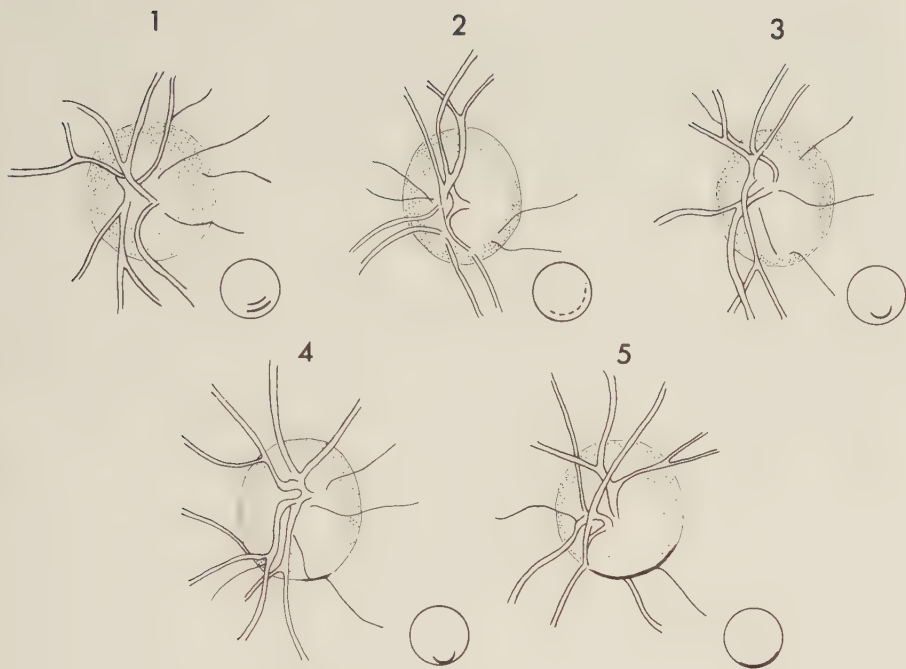


Fig. 3.

Skeleton drawings of the signs used in the classification of the discs. Saucerization (1), Narrow rim (2), Incomplete notch (3), Complete notch (4), Extensive loss of tissue reaching the disc margin (5). The sign referred to is located in the lower half of the disc.

found in 80% on an average. To judge from the appearance of the corresponding disc half, the sensitivity for the detection of field defects averaged 75%. The specificity was 85%.

Compared to similar studies this correspondence was slightly less than that found in examinations of stereophotographs (Douglas et al. 1974; Hitchings & Spaeth 1977). The same correspondence as in the present study was found in a study in which single photographs were used (Hoskins & Gelber 1975).

Comparisons with other studies, however, must be fairly uncertain, and one factor which has to be taken into account is the relative amount of large defects. In the study by Douglas et al.

(1974) the defects consisted to a large extent of arcuate scotomata. Unfortunately, the other studies quoted do not give a clear idea of the size of the defects. Since computerized perimetry is highly sensitive in detection of glaucomatous defects, the present material consisted largely of early cases. With few exceptions the false negatives were small - or even very small - and shallow defects.

An exact correspondence between the optic disc and the visual field cannot be expected. The perimetry was restricted to the central visual field, which means that possible peripheral defects escape detection. Further, in glaucomatous defects there is a more or less pronounced fluctuation from one test session to another, which makes an evaluation based on single test sessions somewhat hazardous (Holmin & Krakau 1979).

In the study by Hoskins & Gelber (1975) a higher accuracy in predicting the state of the visual fields was found in using stereoscopic funduscopy (89%) compared to single photographs (79%). It is probable that a higher accuracy could be achieved with a more elaborate method also in the present study, but apparently even single photographs of average quality, routinely obtained, are valuable as objective documentation of pathological changes in chronic glaucoma.

The consistency between the observers was found to be good. In 61 of the 80 disc halves all three observers agreed on whether the disc halves were normal or pathological. However, in the classification used no clear-cut boundaries can be drawn between different classes. It seemed hard to separate "saucerization" and "normal", and this probably reflects the limitation of a non-stereoscopic method. There was also uncertainty in the separation of "complete notch" and "a more extensive excavation reaching the disc margin". Nevertheless, at least two observers used the same code number in as many as 77 disc halves (96%).

Four disc haemorrhages were recognized by the three observers. They were localized near the poles and no defect was present in the corresponding half of the visual field.

Conclusions

The suggested simple classification of the glaucomatous optic disc was found to be of practical value. The appearance of the optic disc corresponded well with the visual field obtained by computerized perimetry. Single disc photographs, routinely taken, seem to constitute a valuable documentation of pathological changes in glaucomatous discs.

*

The 3 papers already presented were concerned mainly with morphological signs and their association with functional changes. The following 4 papers provide a quantitative evaluation of the development in the visual field.

*

AUTOMATIC PERIMETRY IN THE CONTROL OF GLAUCOMA (IV)

In the treatment of chronic glaucoma it is important to assess a possible deterioration (or improvement) of the visual field. Short term fluctuations of the thresholds in glaucomatous visual fields obtained by manual (Werner & Drance 1977) as well as computerized perimetry (Holmin & Krakau 1979; Gloor et al. 1980) may, however, conceal a slow trend toward decay, or may on the other hand give a deceptive impression of a tendency toward deterioration. Thus for example, three consecutive visual fields with deterioration may be observed, which may lead to therapeutic intervention of some kind. In the evaluation of the effect of this therapeutic measure we have to take into account the fact that a selection of a sequence of falling values from a random series makes probable an improvement of the subsequent values.

The need for a statistical evaluation of series of visual fields is obvious. This need could easily be fulfilled if the results of a sequence of test sessions could be represented by simple numbers, as points in a time series. The numerical results of computerized perimetry makes it possible to construct a simple measure of performance (P). In the report presented in publication IV the aim was to compare this measure with the field chart and to discuss its properties.

Material and methods

Series of visual fields, obtained by computerized perimetry (threshold program) of 24 eyes from 12 patients with chronic glaucoma were analysed. 23 eyes had a visual field defect. The observation period ranged from 2 to 21.5 months and the number of observations varied from 5 to 12.

The results of the perimetry are presented on a field chart in a three-dimensional form as threshold values estimated over a lattice of test points (Fig. 4 a).

Neglecting the localization of defects - which is justified when only a trend has to be traced - it is possible to reduce the representation by one dimension by constructing the distribution of points at the different threshold values (Fig. 4 b).

Proceeding one step further, the representation is made one-dimensional by calculating the sum of the threshold values for all test points ($P_{64} = \sum_{i=1}^{64} x_i$). This measure, which we denote P, is attractively simple and may be used to represent the performance of a test session. In principle, the performance measure resembles that obtained by cutting in paper and weighing profiles and isopter areas at manual perimetry.

Results

Deterioration of the visual field can take place in two ways. Previously existent defects may increase and new ones may appear, or a more widespread decrease in the sensitivity (recognized as a general constriction of isopters when kinetic perimetry is used) may occur.

At examination of the field charts, the defects were considered to be certainly increasing (previously normal points became involved in defect areas in later sessions) in 4 eyes and in another 5 they were possibly increasing.

With the aid of the frequency distribution (Fig. 4 b) a general decrease in sensitivity was found in 6 eyes, 3 of which showed no clear or suspect increase in the defect area.

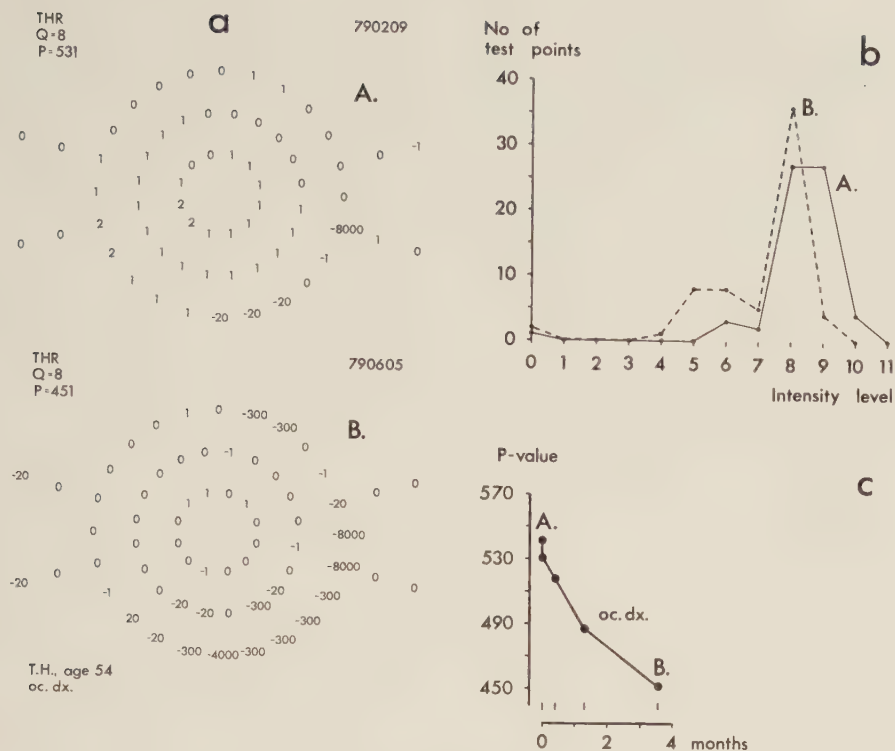


Fig. 4.

Field charts (a). Frequency polygons of thresholds for all 64 test points (b) (increasing sensitivity with increasing number on abscissa). P values plotted against time (c). The field charts and polygons were obtained at A and B.

The series of P values were analysed for a trend. Due to the low number of points in the series only linear regression analysis was performed. The hypothesis to be tested was whether the estimated slope of the linear regression equation (P the dependent and time the independent variable) was significantly different from zero. No significant trend was found in 14 eyes, whereas 7 eyes showed a significant (on the 2% level) trend toward decay (an example in fig. 4 c). In 3 eyes there was a suspected trend toward decay (significant on the 10% level).

When both increase of defects and a general sensitivity decrease observed at examination of charts were considered, the impression of progression, not surprisingly, agreed well with the trend calculated from the series of P values.

A correlation between the short-term fluctuations in the right and the left eye was found. The correlation coefficients r_{RL} between the series of the P values of the two eyes were positive in all cases but one. This covariation between the two eyes could to some extent be attributed to a common slow trend, but when this trend was allowed for the partial coefficients ($r_{RL.T}$) still showed a high correlation.

Discussion

Due to fluctuations in the visual field defects there was uncertainty in deciding progression by a mere examination of a series of field charts. By use of the P values the more or less subjective evaluation could be replaced by statistical tests. The question, however, is whether the P values really contain the relevant information about the development of the visual field. The results of the examination were not incompatible with this opinion although more substantial support is furnished by some theoretical arguments.

The P values are the sum of a number (64) of threshold estimates. In cases of stability the series of P values are distributed around a constant mean. If a number of points give thresholds showing a decreasing or increasing trend, we must expect this trend to be revealed in a series of P values, provided the series is long enough. Since these values can be assumed to be drawn from a fairly normal distribution, the procedure used for testing the hypothesis of a regression coefficient (slope value) different from zero is justified.

Another question is: why not construct a measure by using only threshold values from points in defect areas of the field?

Firstly, a general decrease of sensitivity in the glaucomatous field recognized as constriction of isopters is well known. Secondly, glaucomatous field defects fluctuate in size and shape from one test session to another and the boundaries between defect and normal areas are not clearly defined. We do not therefore consider it justified to base the analysis of a trend in the visual field on the development of certain, arbitrarily selected areas.

The short-term variations can to some extent be attributed to a random scatter of the threshold estimates. The covariation between the right and the left eye, however, indicates some general influence on the ability. This is further supported by a covariation between adjacent points, defect areas being extended or reduced. The dispersion of P differs greatly between individuals and may be caused by i.a. a varying degree of alertness. A prolonged test time has revealed decay or great variability in relative defects, indicating that the test procedure itself affects the results and provoke latent defects (Holmin & Krakau 1979).

In conclusion, since no obvious theoretical or practical objection to the properties of the measure P was found, it seemed usable for summarizing the result of a test session and in the following papers the analysis of the visual field is based on this measure.

VISUAL FIELD DECAY IN NORMAL SUBJECTS AND IN CASES OF CHRONIC GLAUCOMA (V)

and

REGRESSION ANALYSIS OF THE CENTRAL VISUAL FIELD IN CHRONIC GLAUCOMA CASES (VI)

The sensitivity to light decreases with age (Goldmann 1945; Drance et al. 1967). An estimate of the decay in a series of performance values has then to be made allowing for this physiologic effect, the magnitude of which in terms of a regression coefficient (performance units/year) has to be determined.

Normal decay (V)

To survey a great number of normal subjects, results obtained by testing with the screening program were used. With this program the thresholds at 4 points in the 10° circle are determined initially, the rest of the test points then being tested on a supraliminal level. The sum of the first 4 values ($P_4 = \sum_{i=1}^4 x_i$) was used in the study.

Results

In 2998 eyes (age 55-70) - comprising the material in a population survey (Bengtsson & Krakau 1979) - the regression coefficient of P_4 versus age was calculated. The coefficient of regression was -0.166 units/year, which differs highly significantly from zero. Extrapolation from the 4 points to the measure P_{64} (making allowance for one point falling in the blind spot) corresponds to a decay of 2.61 units/year.

One question was: could we preclude the influence of a possible systematic change due to aging in the test system, for example in test light diodes? In order to solve this problem the development of P_4 was studied in 512 eyes retested after about 2.5 years. The decay of P_{64} calculated in the same way as above was 2.20 units/year, which is not significantly different from the decay found in the transversal series.

Another question was if extrapolation from the partial performance value (P_4) to the total P_{64} was justified. Support was furnished by the demonstration of a highly significant correlation ($r_{P_4 P_{64}} = 0.92$) between these two estimates in a group of 43 eyes with normal visual fields.

Thus we concluded that it was justified to use the rate of decay based on the four-point estimate in the transversal series as correction for a physiological decay with age.

Decay in glaucoma cases

These studies were based exclusively on the use of the threshold program. In an effort to minimize the fluctuations in the visual field, e.g. the influence of fatigue, the test sessions were only preceded by testing of the visual acuity. The right eye was always tested first. No change of any pressure-reducing therapy was done during the follow up. Since a learning effect cannot be neglected, all patients were subjected to computerized perimetry at least once previously.

In a preliminary study (V) comprising 54 eyes (38 patients) with glaucomatous field defects, the threshold program was performed at least 3 times with unchanged test conditions. The follow-up period varied from 4 to 24 months. In an attempt to find out whether or not a trend of the performance values was correlated

to successful pressure regulation, the material was divided into three groups (1) 14 eyes without treatment, (2) 29 eyes with a mean IOP < 22 mmHg, with treatment and (3) 11 treated eyes with a mean IOP ≥ 22 mmHg.

The hypothesis that these groups were samples from a population with a normal performance decay with time could be tested by use of a simple sign test, a plus sign being a regression coefficient greater than that found in a normal population, and vice versa. As correction for physiologic decay the mean regression coefficient (-2.61) minus three times the standard deviation, which makes -3.36 units per year, was chosen. In spite of this correction we found in all three groups a preponderance of minus signs, significant at the 1% level for group 2 (mean IOP < 22 mmHg) and for the whole material, and weakly significant (5%) for group 3 (mean IOP ≥ 22 mmHg).

In those 21 eyes in which the number of sessions were at least 5, it is reasonable to test the significance of the individual regression coefficients. Using the same correction for normal decay as above, a significantly lower regression coefficient than the normal one was found in 10 eyes (at the 5% level or less). In 5 eyes it was significant at the 1% level or less.

In the whole material haemorrhages were observed in 8 eyes during the follow up, 4 of which had significantly negative ($p \leq 0.01$) regression coefficients.

The material in this preliminary investigation was heterogenous since both the observation period and the number of test sessions varied considerably. The follow-up time was generally shorter for the group with a higher mean IOP - a consequence of the efforts by ethical reasons to normalize the IOP without too much delay. Nevertheless, the results indicated that the protective effect offered by lowering of the IOP by therapeutic measures is not beyond dispute. This encouraged us to be highly restrictive in instituting or changing pressure-reducing therapy in spite of not too well controlled pressure. Thus - after another two years - we were able to perform a regression analysis of the visual field based on a larger and more homogenous material (VI).

This study comprised 160 eyes in 90 patients (48 to 83 years old, mean 70 years) with at least 5 (range 5 - 7, mean 5.8) separate examinations with a minimum interval of 2 months. The observation period ranged from 13 to 23 months (mean 18.6).

In these cases the regression of performance versus time was calculated for every eye. We could thus study the frequency distribution of the regression coefficients for the whole population and for interesting subgroups.

All patients had a field defect in at least one eye. Since, as a routine, both eyes were tested, a small group (27 eyes) consisted of fellow eyes without field defects. Not surprisingly, a lower rate of decay was found in this group as compared with the group of eyes with defects (mean -0.52 and -1.90 and SEM 0.29 and 0.23, respectively). This difference is significant ($P < 0.005$). The mean decay in the group without defects was slightly stronger than that previously estimated in normals. This is not surprising, since some of these eyes are likely to be on the point of developing defects.

The uncertainty in assessing a trend when only few observations are available was clearly demonstrated when the regression coefficients for the first 3 observations were compared with those based on all (i.e. ≥ 5 ; mean 5.8) observations during the follow-up (Fig. 5). Although the two frequency distributions did not differ significantly with respect to the mean value, the width became considerably smaller when the number of observations was increased (means -1.69 and -1.84, SEM 0.36 and 0.20, respectively).

The observation that the frequency distribution of the regression coefficients becomes narrower with an increasing number of sessions may seem trivial. However, it affords an illustration of the fact that the estimate of a change of trend caused e.g. by some therapeutical intervention is highly uncertain when only few observations are available. Nevertheless, clinical judgements are often based on such uncertain estimates.

The individual regression coefficients for the series of ≥ 5 observations were tested for difference from the physiological decay. On the 5% level (weakly significant), the regression coefficient was lower than normal in 39 eyes (37 with defects) and higher than normal in 7 eyes (5 with defects).

The existence of cases with significant spontaneous "improvements" has clinical implications, and has to be considered in the evaluation of e.g. the effect of therapeutical measures.

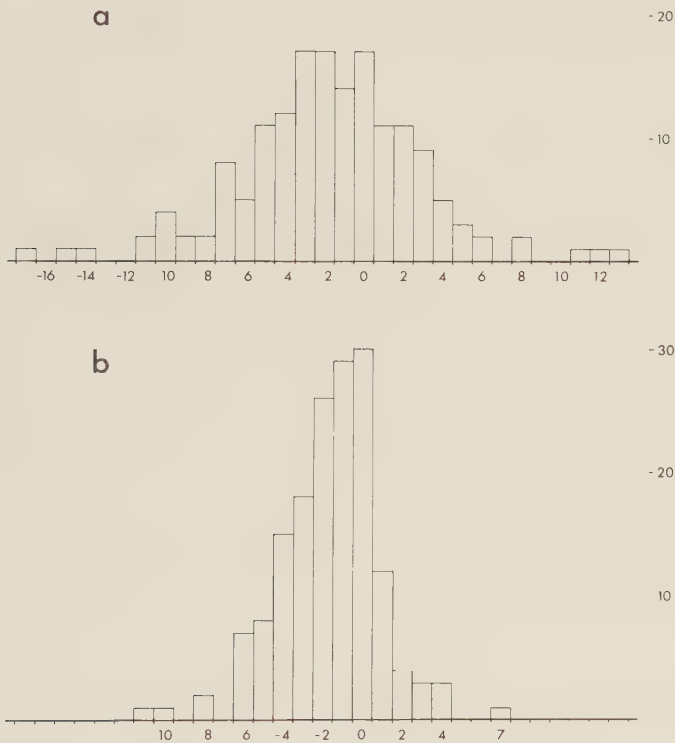


Fig. 5.

The frequency distributions of the regression coefficients for the first three observations (a) and for the whole number of observations (> 5) during the follow up (b). All eyes, i.e. 133 with and 27 without visual field decay are included.

Table 1.

Grouping of 133 eyes with field defects. Number of eyes (N), Mean and SEM of the regression coefficients are given for the groups. "Disc haemorrhages" includes eyes with at least one haemorrhage, and "IOP" refers to the mean IOP during the follow-up period.

	N	Mean decay ($\bar{b}$)	SEM
Born before 1912	73	-1.95	0.32
Born after 1911	60	-1.83	0.33
Male eyes	57	-2.05	0.39
Female eyes	76	-1.76	0.29
IOP below 22	70	-2.04	0.31
IOP above 21	44	-1.95	0.39
Untreated	19	-1.29	0.67
Disc haemorrhages	39	-1.74	0.48
Pseudoexfoliation	22	-2.55	0.61

The material of eyes with defects was divided into groups with respect to sex, age, disc haemorrhages and pseudoexfoliations. Further, groups were formed with reference to the mean IOP. In one the IOP was above 21 mmHg (range 22-33), in another below 22 mmHg (range 10-21). A third group contained the untreated eyes (range 15-25). The regression coefficients (Mean and SEM) for these groups are presented in table 1. The differences between the groups are not statistically significant.

Conclusions

The preliminary study of glaucoma cases gave the general impression of performance values falling with time, even when correction for a normal decay with age was made. This impression was strongly supported by the results of the study based on a larger, more homogeneous material.

A correspondence between significant decay of performance and disc haemorrhages was found in the preliminary study. In the larger, more homogeneous material, no significant difference in the rate of decay was found between groups with and without haemorrhages. Neither was there any difference between groups with fairly well and less well regulated IOP. On the contrary, the narrowing of the regression coefficients (when more observations were at hand) indicated a rather uniform and slow rate of decay in the glaucomatous visual field.

SHORT-TERM EFFECTS OF TIMOLOL IN CHRONIC GLAUCOMA (VII)

Attempts have been made to establish the immediate effect of pressure-reducing agents on glaucomatous field defects. Thus it has been claimed that a reduction of defects may follow the pressure reduction (Paterson 1970, Heilmann 1972). If true, this is a most important observation which might make it possible to apply pressure-reducing therapy where it may be useful. It seemed reasonable to tackle this problem afresh using computerized perimetry. A beta blocker was used as the pressure-reducing agent.

The material consisted of 15 glaucoma patients with relative and incomplete field defects, most of them in a state of decay and showing spontaneous variations in the defects. Presumably there was an opportunity to influence the outcome of the field test.

Computerized perimetry (threshold program) and IOP, systemic blood pressure and pulse rate measurements were performed before and after instillation of timolol (0.5%) or placebo (NaCl 0.9%) in both eyes. All patients were tested 4 times - before and 2 hours after timolol and placebo, respectively. The examinations were carried out in two separate days but since the maximum interval was only 14 days we could leave a decay with time out of account. In 12 eyes already on therapy, the treatment was continued during the study; none was previously on timolol.

All cases had been subjected to computerized perimetry several times before this study and thus the learning effect could be neglected.

The study was carried out in a double-blind manner - neither the patient nor the investigator knew whether placebo or timolol had been used.

The statistical evaluations were based on the mean performance and IOP value for both eyes (except when only one eye - as in 3 cases - had defects).

Results and discussion

Some of the results are presented in table 2.

Table 2.

a) Mean values and SEM for the differences before and after timolol or placebo, the differences before timolol and placebo and the differences between changes after timolol and placebo.

Differences n = 15	Performance		IOP		Pulse rate	
	Mean	SEM	Mean	SEM	Mean	SEM
Placebo day (2 - 1)	-7.8	8.8	0.07	0.47	-5.7 ^x	1.8
First values (3 - 1)	-2.4	9.3	-1.1	0.43	1.7	2.2
Timolol day (4 - 3)	-12.3	9.1	-6.9 ^{xxx}	0.54	-12.0 ^{xxx}	1.3
Tim - Placebo (4 - 3) - (2 - 1)	-4.5	10.0	-7.0 ^{xxx}	0.70	-6.3 ^x	2.3

b) Correlations (total and partial) calculated for the differences between the changes after timolol and after placebo. Correlations in (4-3)-(2-1). Performance (P), IOP (I), Pulse rate (R).

Correlations in (4 - 3) - (2 - 1).

Performance (P), IOP (I), Pulse rate (R)

Perf./IOP		Perf./Pulse rate	
r_{PI}	0.13	r_{PR}	0.46 ^(x)
$r_{PI,R}$	0.23	$r_{PE,I}$	0.49 ^(x)

Both IOP and pulse rate showed significantly greater decreases after timolol than after placebo.

A decrease in P was found both after timolol and after placebo. This decrease was somewhat greater after timolol, but neither difference is significant. Thus, instead of an improvement of P

following IOP reduction which should be anticipated from the pressure-theoretical point of view, we found a positive, though not significant, correlation coefficient.

There was a positive correlation between P and pulse rate which obtains a weak significance when IOP is allowed for. It might then be objected that the reduction of pulse rate affects the P value negatively, thus masking the postulated favourable effect of lowered IOP. This explanation is improbable since the total correlation between P and IOP (r_{PI}) is even slightly lower than the partial correlation coefficient ($r_{PI,R}$).

Even if the pressure reduction had no effect, the random variations make some cases appear as "improvements" and others as "deteriorations". Why could we not accept those eyes whose performance values improved after timolol as "truly" improved?

The results from the other three examinations provide a rough idea of the dispersion of P in the individual eye. We found the P values after timolol inside or near the range of the three values obtained without influence of timolol. This simple range-statistical argument indicates that we have no right to consider these values favourably influenced by the drug. Furthermore, 17 eyes in this report were also included in the larger glaucoma material presented in publication VI. The individual correlation coefficients in these 17 eyes between performance value and IOP show no consistency with the effects of pressure change in the present series: positive and negative correlation coefficients were randomly associated with improvement or decay (unpublished).

Conclusions

A significant decrease of IOP and pulse rate was found two hours after topical timolol. No support for the idea that a modest reduction of IOP by topical timolol favourably influences the visual field was found. There were indications that a reduction of pulse rate is connected with a reduction of the visual field performance.

GENERAL DISCUSSION

In chronic glaucoma the morphological changes of the optic disc and the functional deficiencies revealed by perimetry are closely and logically connected. Loss of neural tissue is reflected as defects, which in the early stages are located primarily in the central field (Aulhorn & Harms 1967). Such defects, however, may have a different etiology. A correct evaluation of the optic disc and the visual field is a prerequisite for detecting glaucoma cases.

In publication III, which is concerned with the morphological changes and their relation to visual field changes, a good agreement between these two symptoms was demonstrated. A simple classification of disc changes seemed to be of practical value.

In cases spotted by computerized perimetry in a population survey (publication I) a high correspondence between disc and field changes was found. The findings during a follow-up further convinced us that these cases were really to be considered "true" glaucomas. Signs of activity in the glaucomatous process in the shape of disc haemorrhages or progression of field defects were found in 9 out of 10 cases observed for more than one year.

The incidence of disc haemorrhages in this group was remarkably high, and in fact indicated that it might be reasonable to regard disc haemorrhages as the rule in glaucoma. Over the last ten years the connection between these two conditions has increasingly attracted attention, and studies on the coincidence have shown that disc haemorrhages are not an uncommon sign in glaucoma (Susanna et al. 1979, Gloster 1981). Until now, cases with haemorrhages have nevertheless been a minority among glaucoma cases.

Our results, based on a material of 1511 persons aged between 55-70, also showed that disc haemorrhage might be a very specific sign of glaucoma. This is in accordance with Kottler & Drance (1976), who found no single case with disc haemorrhages among 100 patients with systemic hypertension or cardiac abnormalities.

It has been suggested that haemorrhage is a symptom of an acute ischaemic lesion and is associated with stepwise progression of visual field loss (Begg et al. 1970,1971). In our material we found no support for a close relationship between haemorrhage and defect increase. Even large or recurrent haemorrhages generally appeared and disappeared without leaving any immediately detectable traces in the visual field or in the optic disc.

The occurrence of haemorrhages in otherwise apparently normal areas of the neural rim and the tendency for the haemorrhages to shift from a polar (in the early stages) to a more temporal location (in more advanced cases), made the denotation of haemorrhages as "forerunners" in the glaucomatous process more likely. This idea has been supported by Airaksinen et al. (1981), who by use of serial stereophotographs were able to show that disc haemorrhages may precede retinal nerve fibre defects by several years.

The relation between the IOP and disc haemorrhages is obscured by the fact that glaucoma cases are treated in order to reduce the pressure. Furthermore, the haemorrhages are detected days or weeks after they have occurred, and the pressure recorded at the detection is consequently a dubious measure of the pressure at the onset of haemorrhages. However, we found no indications that pressure reduction provides a protection against haemorrhages. Nor did it seem likely that they were caused by a high IOP.

In glaucoma control, short-term fluctuations of thresholds may conceal a slow trend toward decay. The need for a statistical evaluation of series of visual fields is obvious.

In computerized perimetry the results are given as numerical values, which made it possible to construct a simple measure of performance (P). Linear regression analysis of series of visual fields could thus be performed. By means of this performance measure the physiologic decay with aging was estimated in a normal population and used as correction when the P value was applied to series of fields of glaucoma cases.

A preliminary study of glaucoma cases gave the general impression of performance values falling with time. This impression was strongly supported in the analysis of a material of 160 eyes of

glaucoma patients, who were followed during an average of 18.6 months with at least 5 observations.

The uncertainty in assessing a trend when only a few observations are available was demonstrated. When we changed from 3 to ≥ 5 observations in a series, the frequency distributions of the regression coefficients became more concentrated. They gathered around a mean of about - 2 (performance units a month), which is significantly higher than the normal decay. This indicates a rather uniform and slow rate of decay in the glaucomatous visual field.

No difference in mean decay was found between subgroups formed with respect to age, sex and pseudoexfoliations. Neither were there any differences between groups with fairly well and less well regulated IOP.

In a comparison of chronic glaucoma cases in which a disc haemorrhage is noted with glaucoma cases without haemorrhages, Drance et al. (1977) found a greater incidence of progression of the visual fields in those with haemorrhages. In our material of 133 eyes with glaucomatous field defects disc haemorrhages were observed during the follow up in 39 eyes. A significant trend toward decay was found in the group with haemorrhages, but this did not differ from the whole group.

The dispersion of the P values differs between individuals. To assume a variation in the patient's ability or alertness seems reasonable but is unsatisfactory as an explanation. During the search for some factor which might influence the variation of P, the immediate effect of a decrease of IOP by timolol was investigated. We were surprised to find a positive (though not significant) correlation between IOP and visual field performance. Certainly some cases might appear as improved, but a simple range statistical analysis showed that there was no reason to regard them as favourably influenced by the drug.

A covariation in short-term variations of P between the right and the left eye was demonstrated in publication IV. We found a positive (weakly significant) correlation between the P value and the pulse rate (VII). Correction for this might reduce the

dispersion of P values, thus making estimates of decay more reliable. Any factor which reduces the dispersion when allowed for is highly important since lower dispersion implies a significant trend obtained more quickly.

*

Most authors stress the importance of pressure reduction even at moderate pressure levels, but there seems to be no convincing evidence that this treatment in glaucoma cases is really effective. A comparison between previous studies and the present one is hardly rewarding due to differences in the demands on method standardization, definition of glaucoma, and analysis of the results.

Since the present studies indicate a slow decay of the visual fields, unresponsive to pressure reducing therapy in glaucoma (a conclusion which refers to a limited pressure range), complementary studies are desirable. Contrary to Chandler, who in a much quoted paper (1960) advocates the detailed study of a small number of selected cases as more valuable than a statistical analysis of a large number of cases, the present author would like to stress the need for long-term prospective randomized studies in order to assess the effect of conventional therapy in glaucoma.

GENERAL CONCLUSIONS

The present studies are concerned with the correspondence between disc findings at ophthalmoscopy or fundus photography and the outcome of computerized field testing in chronic glaucoma.

The importance of disc haemorrhages as a sign of high specificity and sensitivity is demonstrated.

The course of the functional damage could be followed and tested by means of computerized perimetry.

By applying ordinary statistical tests it was found that glaucoma cases subjected to pressure reducing therapy still show a decay of the visual field significantly higher than the normal decay with age.

This decay was independent of the IOP level. The development of the visual fields if the IOP had been allowed to rise to extreme levels or if it had been reduced to very low values was not covered by the present studies.

It was not possible by means of pressure reduction induced by a topically applied beta blocker to select cases suited for pressure reducing therapy. It is suggested, however, that general circulatory factors may affect the visual field performance.

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